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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,238	01/19/2006	Pnina Fishman	FISHMAN19B	9164

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EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	PAPER NUMBER
1657	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,238	FISHMAN ET AL.	
	Examiner	Art Unit	
	SATYENDRA K. SINGH	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 (groups I and II) have been canceled by applicant's current amendments to claims.

Claims 15-20 (elected invention of group III, as currently amended) are examined on their merits in this office action.

Election/Restrictions

Applicant's election of **group III** (claims 15-20; drawn to a method for selecting a subject suffering from a certain inflammatory disease) in the reply filed on June 16th 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, and did not clearly state on the record whether the election was done with or without traverse, this election has been treated as an election **without traverse** (MPEP § 818.03(a)).

Claim Suggestions

Claim 19 recites the limitation of "**IB-MECA**", presumably an abbreviated version of a chemical compound's name. Applicants are requested to recite full **chemical name** of the compound in the claim to help maintain clarity of the invention claimed and examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 15-20 are rejected under 35 U.S.C. 112, second paragraph, as being **indefinite** for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Claim 15 (as currently amended) recites the invention as "a method for selecting a subject suffering from a certain inflammatory disease, to receive anti-inflammatory therapeutic treatment that **comprises** administering to the subject an A3 adenosine receptor (A3AR) agonist, the method **comprising** determining the level of expression of A3AR in the white blood cells (WBCs) of the subject and selecting the subject to receive said anti- inflammatory therapeutic treatment if said level is above a predetermined level". It is unclear as to what the actual invention is being claimed as presented by applicants. Instant claim 15 encompasses **a method of treatment**, i.e. "to receive anti-inflammatory therapeutic treatment that comprises administering to the subject an A3 adenosine receptor (A3AR) agonist" who is "suffering from a certain inflammatory disease", as evidenced by the subject matter of the dependent claims 16-20 as claimed, that also comprises a patient screening method or assay method, i.e. "comprising determining the level of expression of A3AR in the white blood cells (WBCs) of the subject and selecting the subject to receive said anti- inflammatory therapeutic treatment if said level is above a predetermined level". Therefore, it is unclear as to what exactly is being encompassed (metes and bounds) by the invention as currently presented by applicants.

In addition, claim 15 recites the limitation "if said level is above a **predetermined level**", which is confusing. The instant disclosure fails to clearly define such term, and as to what exactly it encompasses in the context of the levels of A3 adenosine receptor (A3AR) in white blood cells (WBCs) of subjects tested. It is unclear as to how such "predetermination" is made, and what kind of subject populations are used to arrive at

such a "predetermined level" of A3AR, as claimed. Therefore, one of ordinary skill in the art would not clearly understand as to how to meet the limitation as recited in the instant invention. Appropriate explanation/correction is required.

For examination purposes herein, the instant claims have been interpreted as a method of treating inflammatory diseases including autoimmune diseases (such as psoriasis, rheumatoid arthritis, asthma, etc.) that comprises selecting the subject and administering an agonist of A3AR to the subject suffering from said disease, as recited in claims 15-20.

2. Claims 16 and 17 recite the limitation "said sample of WBC" and "the inflammatory state" in the respective claims. There is insufficient antecedent basis for these limitations in the respective claims. Appropriate correction is required.

3. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being **indefinite** for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 19 recites the limitation "**an anti-inflammatory amount**" of IB-MECA, which is confusing. It is unclear as to what exactly is encompassed by the term "anti-inflammatory amount" of an agonist IB-MECA because such an amount will variously depend on various factors (i.e. variables) for example, the type of the inflammatory disease, the type of subject population, the stage and severity of said disease, the physiological status of the subjects, routes of administration, types of formulations comprising IB-MECA, etc. to name a few. Since, instant disclosure does not provide a clear definition of the term, the recitation of said limitation renders the claimed invention indefinite. Appropriate correction/explanation is required.

As per MPEP 2173.05(b)-REFERENCE TO AN OBJECT THAT IS VARIABLE MAY RENDER A CLAIM INDEFINITE- A claim may be rendered indefinite by reference to an object that is variable. For example, the Board has held that a limitation in a claim to a bicycle that recited "said front and rear wheels so spaced as to give a wheelbase that is between 58 percent and 75 percent of the height of the rider that the bicycle was designed for" was indefinite because the relationship of parts was not based on any known standard for sizing a bicycle to a rider, but on a rider of unspecified build. Ex parte Brummer, 12 USPQ2d 1653 (Bd. Pat. App. & Inter. 1989).

Claim Rejections - 35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement requirement**. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or **use** the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)).

Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons of record:

Instant claims have been interpreted as being directed to a method of treating subjects suffering from "a certain inflammatory disease" that comprises selecting a subject as specifically recited in claim 15, and administering to the subject an A3 adenosine receptor (A3AR) agonist (see also 112-second rejection of record).

At issue is whether or not the claimed invention ("a method for selecting a subject suffering from a certain inflammatory disease, to receive anti-inflammatory therapeutic treatment that **comprises** administering to the subject an A3 adenosine receptor (A3AR) agonist, the method **comprising** determining the level of expression of A3AR in the white blood cells (WBCs) of the subject and selecting the subject to receive said anti-inflammatory therapeutic treatment if said level is above a predetermined level")

would function for the intended treatment of **any inflammatory disease**, including inflammatory disease such as psoriasis, rheumatoid arthritis, asthma, and other autoimmune disease (see instant claims 17-20, and pages 6-8 of instant disclosure, in particular) in **any subject** suffering from said inflammatory disease.

The Nature of the Invention

The nature of the invention is such that it would require "administering" to a subject (encompasses any administration route such as inhalation, oral, intravenous, intraperitoneal, etc.) suffering from any "inflammatory disease" (autoimmune diseases, such as psoriasis, rheumatoid arthritis, asthma, etc.) an A3 adenosine receptor agonist (such as IB-MECA; see dependent claim 19, in particular) in an "anti-inflammatory amount" (not specified in the claim; see instant claim 19, in particular), wherein the subject has been selected by determining the level of A3AR in a sample of while blood cells (any type of WBCs) from the subject, which is above a "predetermined level" (see instant claim 15, in particular).

The state of the prior art and the predictability or lack thereof in the art

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The invention as claimed is directed to a method of using an agonist for A3 adenosine receptor such as IB-MECA in an "anti-inflammatory amount", for the treatment of autoimmune diseases such as psoriasis, rheumatoid arthritis and other unspecified inflammatory diseases, wherein the selection of the subject suffering from said inflammatory disease is done by

determining the level of A3AR in a sample of any type of WBCs from said subject and selecting the subject if said level is above a "predetermined level".

The state of the prior art indicates that an effective treatment for inflammatory diseases such as psoriasis, rheumatoid arthritis, and/or other autoimmune disorders, is currently known to be highly unpredictable and challenging. The state of the art indicates multiple etiologies, triggering factors, mechanisms of pathogenesis, and reasons (such as genetic, physiological, environmental, etc. and combinations thereof) for the development of clinical symptoms for each of said inflammatory diseases leading to the said conclusion for the unpredictability in their treatments. Taking a well studied inflammatory disease, **psoriasis, for example**, the recent disclosures in the medicine art (see Nickoloff & Nestle, 2004; [U], and Nickoloff et al, 2007; [V]; see abstracts from each article, in particular) clearly indicate that though, being an ancient and universal inflammatory disease, to date the cause of psoriasis remains unknown (see Nickoloff & Nestle, page 1664, left column, in particular), and there is no cure (see Nickoloff & Nestle, page 1665, left column, in particular) available so far. This is clearly evident by the disclosure of Nickoloff & Nestle (see page 1665, left column), wherein the pathophysiology of psoriasis is characterized as follows:

> *"As one considers hypotheses for psoriasis, it is important to recognize at least three unique and characteristic features of this enigmatic disease: (a) Psoriatic plaques represent highly localized sites of dysregulated growth and inflammation, yet these sites almost never develop into, or harbor, malignant clones of keratinocytes, melanocytes, or T cells (5); (b) Despite significantly altered barrier function due to aberrant epidermal cell differentiation, psoriatic plaques are highly resistant to bacterial, viral, and fungal infections (6); (c) Psoriatic plaques, either spontaneously or after various treatments, can revert back to symptomless or apparently healthy skin, with little or no trace of pre-existing disease activity."*

In addition, it is clear from the review provided by Nickoloff & Nestle (see page 1672, "*future directions*", in particular) that although there are many avenues of immunobiology being currently explored to find an effective treatment of the various forms and presentations of this enigmatic disease, we still lack a cure, and the outcome of current treatments of psoriasis remain unpredictable. As evidenced by the disclosure of Nickoloff et al (2007; [V]; see page concluding remarks on page 572, in particular), the cytokine and chemokine networks and their interplay involved in the pathogenesis of psoriasis are currently being explored, and the importance of these mediators of inflammation that seem to play important roles in the pathophysiology of psoriasis are, at the very best, still experimental and will require further experimentation and clinical evaluations:

> "In conclusion, there is no question that many cytokines and chemokines contribute to the initiation and maintenance of psoriatic plaques. It seems like just about every month a new signal transduction pathway linked to cytokines and chemokines emerges from either animal models or human tissue samples. Although psoriatic plaques do not behave or progress to a malignant end point, it is even possible that agents used in the oncology clinic such as the tyrosine kinase inhibitor imatinib (eg, Gleevec, Novartis, Basel, Austria) may be of benefit in complex chronic inflammatory disease (eg, rheumatoid arthritis).69 Whether the primary cellular target within psoriatic plaques is the macrophage, dendritic cell, T cell, mast cell, neutrophil, keratinocytes, fibroblast, or endothelial cell remains to be deciphered by further mechanistic studies involving relevant animal models, human clinical trials, and the use of selective inhibitors mixed with a pinch of serendipity.70-72"

The state of the art for the treatment of asthma (a chronic inflammatory lung condition that includes bronchial and allergic asthma) and its clinical management has been summarized recently by Gillissen (2004; [W]), wherein the author clearly discloses the difficulties in the treatment and management of the patients (see pages 593, 594, and 596, left columns, in particular), and the fact that, at the present time, there is no cure for asthma, and all attempts are mainly geared toward effective management of

symptoms that can help reduce the impact of asthma on quality of life and morbidity (see page 592, right column, in particular).

Similarly, the state of the art for the treatment of inflammatory diseases such as **rheumatoid arthritis** (see recent disclosure provided in the form of a systematic review by Donahue et al, (Donahue et al, [X]; see page 1, "*Summary*", and page 9, "*Discussion*", in particular) clearly indicate the fact that "the comparative effectiveness of rheumatoid arthritis therapies is uncertain" and has been summarized by Donahue et al as follows:

> "Several therapies are available for persons with rheumatoid arthritis; no regimen is clearly better than another. Combination therapies improve response rates in patients previously receiving monotherapy, but available evidence does not allow firm conclusions about which combination strategy is best. Future studies, including those with good applicability to patients seen in community practices, will be useful; researchers should plan to perform subgroup analyses a priori in older patients and patients with comorbid conditions. Long-term adverse event studies, particularly with the newer agents, will help clinicians and patients better weigh the benefits of these drugs."

In addition, emerging adenosine receptor agonists and their potential application in the treatment of rheumatic diseases and cancer have been recently reviewed by Gao & Jacobson (2007; [U2]), wherein they clearly point out the exploratory stage and nature of the development of agonists (including A3AR agonist such as IB-MECA) that need further extensive studies and clinical trials in humans and other model mammals before they can be of significant use in treating various inflammatory diseases, especially as it is unclear if the behavior of the A3AR activation will be similar or different *in vitro* and *in vivo*, and because "it is suggested that the pro- or anti-inflammatory roles of A2B and A3AR might depend on tissues, inflammatory stages and types" (see page 480, right column 2nd paragraph, figure 1, page 484, right column, 2nd paragraph, page 485, right

column, last paragraph, in particular). Gao & Jacobson summarize the state of adenosine receptor agonists as follows (see page 488, right column):

> "The abundance of the A3ARs in inflammation-related blood cells, such as neutrophils and eosinophils, may suggest a role for the A 3 AR in inflammation. However, the pro- or anti-inflammatory role of the A3AR has to be further clarified. Nevertheless, preliminary clinical trial data suggest that the A3AR may be a new promising target for RA. (rheumatoid arthritis). Regarding the anticancer role of some nucleosides or the A3AR, it is still to be further investigated."

Thus, the state of the prior art, as discussed above, clearly suggests the unpredictability involved in the claimed method of treatment of inflammatory diseases (such as psoriasis, rheumatoid arthritis, or asthma; none of these being curable inflammatory diseases as evidenced by the disclosures in the cited prior art), and the fact that under present circumstances, the treatment of said inflammatory diseases in an individual by administering an agonist for A3 adenosine receptor such as IB-MECA, as contemplated and claimed by the instant invention, is not predictable. In fact, factors such as tissue distribution, selectivity, pharmacologic behavior, *in vivo* half-life, correlation between *in vivo* and *in vitro* experiments, and studies using relevant model animals with predictable outcome in humans are needed to clarify the role of various adenosine receptor agonists in order for them to be used as an effective therapeutic alternative for treatment of inflammatory diseases such as rheumatoid arthritis, psoriasis, asthma, etc.,for example.

The amount of direction and guidance present and the presence or absence of working examples:

Given the teachings of unpredictability found in the art, detailed disclosures are required to be present in the specification in order to enable the skilled artisan to practice the invention commensurate in scope with the claims. These teachings are

absent in the instant specification. The courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971).

The instant disclosure provides data from adjuvant-induced arthritis in experimental animals such as rats (see instant disclosure, pages 4-5, in particular). However, the disclosure fails to provide guidance as to how to correlate such data obtained from the experimental animals with the *in vivo* outcome that will translate into an effective treatment of such unpredictable inflammatory diseases in individuals having diseases such as rheumatoid arthritis, psoriasis, asthma, etc. as currently encompassed by the claimed invention. The instant disclosure, as filed, does not provide appropriate guidance as to how to treat an individual having such unpredictable inflammatory diseases as psoriasis, rheumatoid arthritis, asthma, etc. by administering an anti-inflammatory amount of an agonist of A3AR as claimed in the instant invention. Thus, it will require a huge amount of experimentation for a skilled artisan in the clinical art to perform a treatment process such as claimed with a predictable outcome as intended by the applicants.

The breadth of the claims and the quantity of experimentation needed:

Because the instant claims encompass a process of treatment of any inflammatory disease (including highly unpredictable inflammatory conditions such as psoriasis, rheumatoid arthritis, asthma, etc.) in an individual suffering from said disease by administering (through any route of administration) an agonist of A3 Adenosine

receptor (claim 15, not limited to any specific agonist compound) in an "anti-inflammatory amount" (not defined in the instant disclosure), which will vary with the type of disease and patient population, and the severity of the inflammatory disease being treated, in light of the teachings of the unpredictability disclosed in the art discussed above, and because of the lack of sufficient teaching/guidance in applicant's disclosure to overcome those teachings, it would require undue experimentation by one of skill in the art to be able to practice the invention, as currently claimed.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Conclusion

NO claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SATYENDRA K. SINGH whose telephone number is (571)272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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